REMARKS/ARGUMENTS

Claims 19-22 are pending in the present application. Claims 1-5 and 7-18 are withdrawn and claim 6 is canceled by previous Amendment. By this Amendment, Applicant has amended claim 19. Support for the amended claim can be found throughout the specification and claims as originally filed. Entry and consideration of the amended claim presented herein is respectfully requested. Accordingly, claims 19-22 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 19-22 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Accordingly, claim 19 has been amended to clarify that the term "concentration" was used to describe an amount of compound-of-interest per milliliter of liquid excipient. By this Amendment, the term "concentration" has been removed and replaced by the term "amount." In addition, step (b) has been incorporated into step (a) to further describe the preparation of an array method step. Finally, the claim has been amended to specify that the excipient is dispensed into wells of the array.

Claims 19-22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Cheng *et al.* (US Patent No. 6,957,151 B2) in view of Popli *et al.* (US Patent No. 5,616,621) and Desrosiers *et al.* (US Published Application No. US 2003/0119060 A1). Applicants respectfully traverse the rejection.

The Cheng reference discloses systems and methods for aqueous solubility prediction. The Examiner cites Tables 1-3 and paragraphs [0035]-[0038] of the Cheng reference as teaching a method for determining and ranking the solubility of a pharmaceutical drug in different concentrations and types of excipients. In fact, the Cheng reference teaches a method for predicting equilibrium aqueous solubility. The "prediction" of solubility by mathematical calculation and the "determination" of solubility by actual measurement cannot be construed as equivalent or even interchangeable techniques. The pending claims are not drawn to the mathematical prediction of solubility, as in Cheng, but to the actual measurement of solubility. Moreover, while the Cheng reference explicitly describes the prediction of "aqueous

solubility" in paragraph [0036], the currently pending claims are drawn to solubility measurement in "non-aqueous samples." Cheng describes the importance of descriptors in its methods, some of which are based on the number of hydrogen bond donors and acceptors in the molecular structure of the compound-of-interest. Such characteristics are critical for aqueous solubility determination as water can act as both a hydrogen bond acceptor and as a donor. However, the importance of hydrogen bonds in non-aqueous solubility can be significantly less than for aqueous solubility. Many non-aqueous liquid excipients (e.g., castor oil) will have hydrogen bonding properties that are quite distinct from that of water. The formation of micelles, for example, would likely cause significant problems for the predictive power of the methods disclosed in Cheng. In summary, aqueous solubility and formulation solubility are clearly distinct.

The Cheng reference describes methods for the prediction of aqueous solubility. However, the pending claims are drawn to the experimental determination of non-aqueous solubility where an excipient is dispensed in a volume of less than 250 microliters and has a viscosity greater than 100 centipoise. There is no support in any of the cited references, or any combination thereof, for the dispensing of an excipient with a viscosity greater than 100 centipoise in a volume of less than 250 microliters. The only cited reference that describes viscosity is the Popli reference. The Popli reference describes compositions comprising taste masking excipients for the administration of unpleasant tasting compounds. Popli *et al.* describe much larger composition volumes of 5 milliliters, for example in claims 4 and 5, and do not describe any dispensing methods. However, the current invention is specifically drawn toward small samples volumes, hence the limitation of "less than 250 microliters." The use of small sample volumes enables the investigation of many excipient combinations while minimizing the amount of compound-of-interest required, which can be difficult or costly to make in larger amounts. The present invention overcomes the challenges of limited amounts of the compound-of-interest, the use of viscous excipients which are difficult to dispense reproducibly in small volumes, and the screening of many excipients and excipient combinations in order to optimize liquid formulations for several properties, including formulation solubility.

According to paragraph [0035] in Cheng, the disclosed methods may be used to screen-out compounds which possess undesirable solubility characteristics. The instant invention discloses methods which attempt to do precisely the opposite. The pending claims describe methods for screening excipients and combinations of excipients in an effort to facilitate formulation and development of a pre-selected compound-of-interest.

The Desrosiers reference describes high-throughput screening of drug candidates for various properties including solubility. This reference describes the use of an array format in the screening process. The Examiner uses the Desrosiers reference to find the array aspect of the instant claims obvious when considered with the Cheng reference. However, as stated above, the Cheng reference describes a mathematical calculation. The combination of a mathematical exercise and a physical array format is nonsensical. Even if such a combination was, in fact, obvious, it does not render the currently claimed invention, experimental methods comprising the dispensing of less than 250 microliters of non-aqueous excipients with a positive displacement pump, obvious.

The Examiner has failed to indicate any art which teaches or suggests several of the limitations explicitly described in the pending claims, including: a screening method designed for the use of non-aqueous excipients with a viscosity greater than about 100 centipoise, the use of a positive displacement pump, and the dispensing of less than 250 microliters of an excipient. As such, the Examiner has not met his burden of establishing *prima facie* obviousness. MPEP 2143.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Applicants aver that all pending and withdrawn claims were commonly owned as of the date of invention for each claim.

Respectfully submitted,

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